

**UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY
CAMDEN VICINAGE**

**IN RE: VALSARTAN, LOSARTAN,
AND IRBESARTAN PRODUCTS
LIABILITY LITIGATION**

This Document Relates to All Actions

MDL No. 2875

Honorable Robert B. Kugler,
District Court Judge

Oral Argument Requested

**MEMORANDUM OF LAW IN SUPPORT OF DEFENDANTS'
JOINT MOTION TO EXCLUDE THE OPINIONS OF
STEPHEN LAGANA, M.D.**

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Defendants Executive Committee, on behalf of all Defendants in this litigation, respectfully submits this Memorandum of Law in Support of Defendants' Joint Motion to Exclude Opinions of Dr. Stephen Lagana, pursuant to Federal Rules of Evidence 104, 403, and 702 ("Motion").¹

INTRODUCTION

Stephen Lagana, M.D. is an anatomical pathologist with no education, training, experience, or specialized knowledge in conducting epidemiologic investigations examining the ability of a particular chemical agent to cause cancer. His education, training, clinical experience, and research experience is all in the field of pathology. He analyzes slides to diagnose or grade diseases and researches gastrointestinal and liver pathology. (Lagana Rep. at 2).² Yet Plaintiffs have designated Dr. Lagana to opine as to whether ingestion of NDMA or NDEA as a contaminant or impurity of valsartan can cause cancer in humans at the levels documented in the testing that has been performed. (Lagana Rep. at 1). Plaintiffs have failed to satisfy their burden of showing that Dr. Lagana's opinions and conclusions are qualified, reliable, and fit the general causation question before this Court. Accordingly, his opinions should be excluded in their entirety.

¹A copy of Plaintiffs' Designation of Experts and Opinion Testimony, served July 12, 2021 (hereinafter, "Plaintiffs' Designations"), is attached as Ex. A.

²A copy of Dr. Lagana's Expert Report (hereinafter, "Lagana Rep." or "Report"), is attached as Ex. B.

First, Dr. Lagana's opinions and methodology are unreliable. Despite the claims to the contrary in his Report, he did not employ his "standard methodology" or anything like it. Most critically, Dr. Lagana failed to proceed from a neutral or null set starting point; instead, he put his thumb on the scale by applying a presumption that if a patient took valsartan and developed cancer, it must be assumed the valsartan caused the cancer. (Lagana Rep. at 33).

From that biased and unscientific starting point, Dr. Lagana then failed to follow the standard methods and practices of pathology that he brings to his everyday clinical and research practices. Instead, he undertook a review of a limited subset of epidemiology literature outside his field of expertise and on subjects unfamiliar to him and supplied a book report of his findings. That is not a method he has ever employed in his career outside of this specific litigation context. Further, he applied that methodology selectively, failing to consider critical literature and scientific issues that would bear materially on his ultimate conclusions. Due to both his biased starting assumption and his unreliable methodology, all Dr. Lagana's opinions are inherently unreliable, lack scientific rigor, and do not fit the general causation question in this case.

Finally, Dr. Lagana's choice to employ an unreliable methodology and his application of that unreliable methodology to unreliable and incomplete data are not surprising because Dr. Lagana is not qualified to offer his disclosed opinions. In

formulating his opinions, Dr. Lagana undertook no inquiry within his field. He received and considered no pathology slides, undertook no pathology analysis, reviewed no pathology literature, and performed no pathology research. His education, training, specialized knowledge, and clinical or research experience played no role in forming his opinions, or in the methods employed to arrive at his conclusions. Nor did he call upon his prior experience with NDMA or NDEA—because he has none. In short, Dr. Lagana is not qualified to offer his general causation opinions.

For these reasons, Dr. Lagana should not be permitted to opine on general causation before the Court or any jury, because his opinions and testimony are unqualified, based on unreliable support, and ultimately fail to address—much less answer—the general causation question at issue. Accordingly, Dr. Lagana’s opinions must be excluded in their entirety. This brief expressly incorporates the facts and law set out in the Motion to Exclude Dr. Stephen Hecht.

SPECIFIC OPINIONS TO BE EXCLUDED³

Defendants move to exclude Dr. Lagana’s opinions and testimony in their entirety, including the following general causation opinions:

³Defendants reserve the right to move to exclude or limit this expert witness’s opinions on grounds other than those set forth herein if those grounds become available subsequent to the filing of this Motion by virtue of the Court’s rulings, any

- The levels of NDMA and NDEA in the allegedly contaminated valsartan “caused an unreasonably dangerous risk to those who ingested it.” (Lagana Rep. at 33).
- Individuals who ingested valsartan containing NDMA and NDEA “have an increased risk of cancer, . . . without reference to individual predispositions or concurrent risk factors.” (*Id.*).
- The presumption that cancer was caused by exposure to a carcinogen, including the opinion that “for any patient who develops cancer and is known to have a significant exposure to a probable human carcinogen . . . it should be assumed that the carcinogenic exposure at least increased the risk or contributed to the subsequent cancer, unless there is a convincing body of evidence to suggest that the carcinogenic insult is null with respect to the specific cancer in question.” (*Id.* at 11).
- “From a medical and scientific perspective, anyone who consumed such products has been harmed, irrespective of whether they have suffered a clinically manifested outcome to date, because the ingestion of the contaminated valsartan has increased the risk that they will develop cancer at some point during their lives.” (*Id.* at 33).

additional discovery that may take place in this case, or supplementation of this expert witness’s disclosure or report.

- “[S]ome number of those people likely already have and/or will in the future develop cancer as a result.” (*Id.* at 1).
- There is “evidence [that] suggests NDMA is absorbed into the blood,” and therefore can cause cancer in any organ. (*Id.* at 22).
- “[I]t is probable that individuals who are predisposed to cancer for any reason (genetic or environmental) have an even greater likelihood of developing cancer following and in part as a result of ingestion of NDMA or NDEA at the levels established for the contaminated valsartan.” (*Id.* at 5).
- “[T]o the extent NDMA is discussed herein, the conclusions as to NDMA apply to NDEA as well, unless otherwise indicated.” (*Id.*).

Dr. Lagana also admits he is not an expert in epidemiology, biostatistics, cancer biology, toxicology, hypertension, molecular pathology, oncology, pharmacology, FDA, or regulatory issues. (Lagana Dep. at 64:16-24, 123:15-25, 137:8-10, 157:18-23, 163:15-164:4, 208:18-20, 235:19-236:16, full deposition transcript attached as Ex. C). By his own admission, Dr. Lagana lacks the education, training, or experience to offer opinions on these subject matters and should not be permitted to testify on such topics.

FACTUAL AND PROCEDURAL BACKGROUND

Defendants hereby adopt and expressly incorporate by reference the “Factual and Procedural Background” set forth in the Memorandum of Law in Support of Defendants’ Joint Motion to Exclude the Opinions of Stephen Hecht, Ph.D.

LEGAL STANDARDS

In addition to the legal standards set forth herein, Defendants incorporate by reference the section entitled “Legal Standards” set forth in the Memorandum of Law in Support of Defendants’ Joint Motion to Exclude the Opinions of Stephen Hecht, Ph.D.

Under Federal Rule of Evidence 702, this Court performs a “gatekeeping function” to ensure that all expert testimony is both relevant and reliable. *See In re Paulsboro Derailment Cases*, 746 Fed. Appx. 94, 98 (3d Cir. 2018) (Vanaskie, J.) (citing *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 589 (1993)). It is Plaintiffs’ burden alone to show Dr. Madigan’s testimony is admissible. *See Warren Distributing Co. v. Inbev USA L.L.C.*, 2010 WL 2179167, at *3 (D.N.J. May 26, 2010) (Kugler, J.) (citing *Kannankeril v. Terminix Int’l, Inc.*, 128 F.3d 802, 806 (3d Cir. 1997)).

“Rule 702 embodies a trilogy of restrictions on expert testimony: **qualification, reliability, and fit.**” *Ruggiero v. Yamaha Motor Corp., U.S.A.*, 778 F. App’x 88, 93 (3d Cir. 2019) (emphasis added) (quoting *Schneider ex rel. Estate of*

Schneider v. Fried, 320 F.3d 396, 404 (3d Cir. 2003)). First, the Court must consider whether the expert is qualified “to render an opinion” based on his or her “specialized expertise.” *In re Hum. Tissue Prods. Liability Litig.*, 582 F. Supp. 2d 644, 655 (D.N.J. 2008) (quoting *Pineda*, 520 F.3d at 244). Though qualification is interpreted liberally, the Third Circuit recognizes an expert who “may be generally qualified” may nevertheless “lack qualifications to testify outside his area of expertise.” *Calhoun v. Yamaha Motor Corp., U.S.A.*, 350 F.3d 316, 322 (3d Cir. 2003). Second, the Court must evaluate the reliability of the expert’s methodology. For an expert to be reliable, his opinions must be based on methods and procedures of science rather than on subjective belief or unsupported speculation. The expert must have “good grounds” for his or her belief. *See In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 732 (3d Cir. 1994) (quoting *Daubert*, 509 U.S. 579 at 590). Third, the Court must consider whether the expert’s testimony will be helpful to the trier of fact. *See Fed. R. Evid. 702(a)*. “The issue of fit ‘is one of relevance and expert evidence which does not relate to an issue in the case is not helpful.’ . . . The standard for fitness is ‘not that high’ but is ‘higher than bare relevance.’” *In re Hum. Tissue Prod. Liab. Litig.*, 582 F. Supp. 2d at 657 (quoting *In re TMI Litig.*, 193 F.3d 613, 670 (3d Cir. 1999); *In re Paoli*, 35 F.3d at 745). An opinion fits and helps the trier of fact when there is a connection between the scientific research or test result to be

presented and the particular disputed factual issues in the case. *Warren Distributing Co.*, 2010 WL 2179167, at *4.

ARGUMENT

I. DR. LAGANA’S OPINIONS ARE UNRELIABLE AND FLOW FROM A FLAWED AND UNRELIABLE METHODOLOGY.

A. Dr. Lagana Formed His Opinions From The Biased And Unscientific Assumption That Causation Exists Wherever There Is Exposure.

This Court could and should exclude Dr. Lagana’s opinions in their entirety, based solely on the completely unscientific and biased starting assumption from which all his opinions flow. Specifically, Dr. Lagana’s Report states “for any patient who develops cancer and is known to have a significant exposure to a probable human carcinogen . . . it should be *assumed* that the carcinogenic exposure at least increased the risk or contributed to the subsequent cancer, unless there is a convincing body of evidence to suggest that the carcinogenic insult is null with respect to the specific cancer in question.” (Lagana Rep. at 11 (emphasis added)).

That premise is wholly unscientific. It is a basic tenet of research science that scientists must begin with and assume the null hypothesis (no causation) and present evidence sufficient to overcome it. *See e.g., Reference Manual on Scientific Evid.*, Third. Ed. (2011) at p. 315 (defining hypothesis test: “the idea is to see whether the data conform to the predictions of the null hypothesis” or are sufficient to “undermine the null hypothesis”). Courts and Plaintiffs’ own experts subscribe to

that tenet. *See, e.g., Smith v. Wyeth-Ayerst Labs. Co.*, 278 F. Supp. 2d 684, 693 (W.D. N.C. 2003) (“the power of a study... refers to the chance that a statistical test will declare an effect when there is an effect to declare or ‘the probability of rejecting the null hypothesis when the alternative hypothesis is right’” (citing Ref. Manual on Scientific Evid.)); Madigan Dep. at 160:15-162:10 (in a data-drive approach “the idea is you want to study the association between A and B... you build a so-called empirical null distribution”). Yet, by his own admission, Dr. Lagana has done precisely the opposite.

Indeed, at his deposition, he stated “I don’t think that one needs to start with the null hypothesis[.]” (Lagana Dep. at 297:12-16). He attempted to justify this by pointing out that the statement in his report is specific to “any patient who develops cancer,” rather than the literature as a whole, but that is immaterial — he began with his thumb on the scale, starting from an unscientific premise. (Lagana Dep., at 298:2-299:19). Dr. Lagana explicitly began his research with an assumption that general causation was proven and then embarked on a literature search intent on finding evidence to support that assumption. Ignoring the dictates of the scientific method and the requirements of Rule 702 and *Daubert*, Dr. Lagana suggests that his *ipse dixit* should be sufficient, testifying that, in some situations “a little bit of common sense” is the better approach. (Lagana Dep. at 295:19-296:12). “Common sense” is not science or a scientific method. It is also legally improper and inadmissible —

Dr. Lagana's approach both reverses plaintiff's burden of proving general causation and renders his entire methodology unreliable. For this reason alone, Dr. Lagana's opinions should be excluded in their entirety.

B. Dr. Lagana Failed To Employ The Same Methodology He Brings To His Research.

Dr. Lagana's biased and wholly unscientific starting premise is grounds enough to exclude his opinions; but, there is more: in order to support the biased assumption from which he proceeded, Dr. Lagana employed an unreliable methodology inconsistent with his own research practices. Then, he selectively applied that methodology to incomplete and unreliable data.

Dr. Lagana's Report opens with this demonstrably false assertion regarding his methodology: "I am basing everything stated herein on the basis of the methodology I apply in my clinical and academic work." Lagana Rep. at 3. Dr. Lagana's subsequent testimony, however, makes clear that he employed none of his standard methods in undertaking his review and rendering his opinions in this case. Dr. Lagana's actual standard methodology consists of reviewing pathology specimens under a microscope, drawing conclusions as to whether they are benign, malignant, inflamed, or normal, and supplying his reports to treaters to render a diagnosis. (Lagana Rep. at 2; Lagana Dep. at 60:21-61:1, 61:12-18, 68:3-25, 79:1-80:2, 162:5-19). He employed none of those methods here, but instead rendered

causation opinions based solely on a review of epidemiology literature—something he never does in his practice. (Lagana Dep. at 106:18-24, 118:20-119:5).

Dr. Lagana’s own prior expert work further confirms he has not followed his standard methodology in this case. Dr. Lagana has worked with Plaintiffs’ counsel once before, in the *Benicar* litigation in 2017,⁴ in which he provided a report opining that Benicar causes organic changes to the small intestine, which is relevant for cancer formation (hereinafter, the “*Benicar* Report,” attached as Ex. D). Dr. Lagana provided a detailed explanation of his standard methodology in the *Benicar* Report:

The diagnostic approach I take to such cases is standardized, and is the approach utilized in my clinical practice...I start with the review of very basic clinical information (generally limited to the presenting symptoms; e.g., diarrhea). I then begin my slide review.

(*Benicar* Report at 2-8).

At his deposition, Dr. Lagana admitted that his methodology with respect to his clinical work has not changed. (Lagana Dep. at 104:16-105:10). In this case, however, not one of his opinions is even remotely linked to “review of basic clinical information” or slide review.

It is abundantly clear that Dr. Lagana’s “standard methodology” does not include research or work on the general causation of cancer. When he does, he bases

⁴ *In re Benicar (Olmesartan) Products Liability Litigation*, Case No. 1:15-md-2606 (D.N.J.).

it entirely on review of the patient's biopsy, which has no bearing on the question of causation. As a clinical pathologist, he does not study or offer opinions on general causation for patients he encounters, and in his day-to-day practice he does not form opinions similar to the one he offers here. (See Lagana Dep. at 120:19-122:7 ("Q: As a doctor, as a clinical pathologist, an anatomic pathologist, you do not do what you did in this case; true? A: ...I haven't produced a document like this [Report] outside of this [case]. Q: this is the first time in this litigation; correct? A: Yeah.")). Asked whether he has ever answered a general causation question in his clinical practice, he admitted "That's not part of my practice." (*Id.* at 107:11-108:14).

It is not surprising that Dr. Lagana employed an unfamiliar and unreliable methodology, here, because he was researching an issue he had never before encountered in his clinical practice. Instead, Dr. Lagana was assigned his research question by Plaintiff's counsel and proceeded accordingly:

Q: In terms of this question, whether ingestion of NDMA and NDEA as a contaminant or impurity of Valsartan can cause cancer in humans, that question, all of your knowledge, research came in litigation; correct?

A: Well, before this started, I certainly knew that NDMA was a potent laboratory carcinogen for animals. As far as how carcinogenic it was or was not for humans, I don't recall having looked at that literature in detail before this litigation.

Q: And that's not an issue in your clinical practice; true?

A: True.

(Lagana Dep. at 54:13-55:5)

Dr. Lagana's use of a litigation-driven methodology far outside his standard methodology, while professing to follow his standard methodology, requires exclusion of his opinions as unreliable. "[W]hen an expert opinion is based on data, a methodology, or studies ***that are simply inadequate to support the conclusions reached***, Daubert and Rule 702 mandate the exclusion of that unreliable opinion testimony." *Amorgianos v. Nat'l R.R. Passenger Corp.*, 303 F.3d 256, 266 (2d Cir. 2002) (emphasis added). When experts depart from their own professed standards or the standards of their field, it is a compelling indicator of unreliability that requires exclusion of their opinions. *See Truck Ins. Exch. v. Magnetek, Inc.*, 360 F.3d 1206, 1213 (10th Cir. 2004) (affirming exclusion of fire investigation expert's opinions where the expert's opinion "did not meet the standards of fire investigation [the expert] himself professed he adhered to"); *Magdaleno v. Burlington N. R.R. Co.*, 5 F. Supp. 2d 899, 905 (D. Colo. 1998) ("In sum, [the expert]'s methodology is not consistent with the methodologies described by the authors and experts whom [the expert] identifies as key authorities in his field."); *see also* Memorandum of Law in Support of Defendants' Joint Motion to Exclude the Opinions of Stephen Hecht, Ph.D. ("Motion to Exclude Hecht"), at section I(A)(2). Dr. Lagana professed to use his "standard methodology" while in reality departing altogether from it because it

could not yield the conclusions he was asked to supply. His opinions are thus inherently unreliable and should be excluded.

C. Dr. Lagana Applied His Unreliable Methodology To Incomplete And Unreliable Data.

Instead of approaching the question in a scientific manner and without forming a conclusion prior to research and investigation, Dr. Lagana hunted for supporting articles, cherry-picking those supporting his pre-formed conclusion. In the process, he ignored key literature and important confounders.

i. Dr. Lagana Fails to Give Weight to Key Epidemiology Literature.

As set forth above, Dr. Lagana did not employ his standard pathology methodology of reviewing tissue samples and diagnosing disease based on molecular information and data. As such, it was particularly important that he consider and assess all of the relevant epidemiologic data to ensure the soundness of his opinions and methodology. Dr. Lagana does not do so. Instead, Dr. Lagana's Report gives short shrift to the two studies that *actually* involve the valsartan at issue in this litigation. *See* Exs. E and F (Gomm, et al. and Pottegard, et al.). The Pottegard and Gomm studies, while cited in Dr. Lagana's Report, are only examined briefly. Dr. Lagana opines that the Gomm study's finding of a nominally significant association with liver cancer is "a canary in a coal mine." (Report, at 26). But Dr. Lagana did not consider or discuss Gomm's key conclusion – finding no statistically

significant association between valsartan use and overall risk of cancer or any other specific cancer. Likewise, Dr. Lagana's only reference to the Pottegard study is to say it "suggest[s]" increased cancer risk in consumers of valsartan. Report, at 27. In fact, the Pottegard study states "the results do not imply a markedly increased short term overall risk of cancer in users of valsartan contaminated with NDMA." Ex. F. That Dr. Lagana chose to gloss over two studies that speak directly to the central question of cancer causation by NDMA/NDEA in valsartan confirms his opinions are unreliable.

ii. Dr. Lagana Completely Ignores Issues of Dose and Duration of Exposure.

Dr. Lagana omits any discussion of the critical factors of dose or timing, even as he opines that the alleged valsartan exposures in this case support a finding of increased risk of cancer. Dr. Lagana agrees it is "likely" that dose impacts risk, and that "looking at the dose and length of exposure are both reasonable things to consider." (Lagana Dep. at 39:11-41:20).

Inexplicably, however, his Report considers neither. Dr. Lagana ignores the *actual* levels of NDMA and NDEA detected in valsartan, preferring instead to base his opinions on dietary and animal studies. (Lagana Dep., at 337:12-21) ("I have looked at the evidence that exists. And that concludes dietary studies which show rather significant potency for NDMA causing cancer. So based on the dietary studies, as well as animal studies, if you're asking me if I can say to a reasonable

degree of medical certainty whether these people have been harmed or not, I absolutely believe they've been harmed.") But Plaintiffs' experts concede that dietary exposures are not the relevant inquiry – retrospective studies based on dietary questionnaires are notoriously unreliable due to recall bias, selection biases and other factors; equally unreliable are the decades-old food tables that were used to estimate the levels of nitrosamine in each food stuff examined. (Etminan Dep. at 142:7-20, 144:20-145:25, 153:8-17, 247:5-249:3; Hecht Dep. at 215:6-217:25 ["just about all of these studies can be criticized for one reason or another"].)

Dr. Lagana admits that the dietary studies cannot be directly correlated to valsartan patients, as the dose and time frame are important considerations. (Lagana Dep. at 335:22-336:16.). He also concedes that the animal studies using large doses of NDMA may be inapposite, admitting "there are differences between animals and humans... And doses might not be easily extrapolated from the one to the other." (Lagana Dep., at 249:6-13).

Further, despite his apparent preference for dietary and animal studies to the human epidemiology data (Gomm and Pottegard), Dr. Lagana simply ignores those dietary studies in which some NDMA doses did not result in observed cancers, overlooking key data that undermine his preferred conclusions. *See also* Motion to Exclude Hecht, at section II(A)(1) (discussing the hierarchy of epidemiological studies). For example, Dr. Lagana's Report does not cite to or discuss studies by

Jakszyn (2011 and 2012) which failed to find associations between dietary nitrosamines and bladder and prostate cancers. (*See* Exs. E and F.)

In sum, Dr. Lagana fails to consider the doses and duration of exposure to NDMA/NDEA actually at issue here; he also ignores the negative findings of the only human epidemiology studies to look at valsartan containing NDMA/NDEA. Instead, he relies on dietary and animal studies that suffer many limitations; except, where those dietary studies fail to find an association — those he ignores, as well. All of this makes clear that his opinions are unreliable. *See Meyers v. Gwin Dredging & Dock, Inc.*, 2005 WL 8175914, at *2 (D.N.J. Dec. 20, 2005) (“The other two studies, which did note statistical significance, did not increase the reliability of the experts’ opinions because one did not mention PCB’s specifically, and the other involved subjects that were exposed to numerous potential carcinogens.”); *See also* Motion to Exclude Hecht, at sections II(A)(1)-(3).

iii. Dr. Lagana Relies Heavily on Inapposite Studies and Ignores Important Confounders.

Dr. Lagana also cites to a study by Hidajat, et al. which involved an irrelevant route of exposure and failed to account for significant confounders of cancer for the subjects of those studies. Specifically, Dr. Lagana relies on Hidajat’s conclusion that cumulative exposure to certain levels of NDMA statistically significantly increases one’s risk of developing certain cancers. (Lagana Rep. at 16-17). Hidajat examined British rubber industry workers who inhaled large quantities of NDMA and other

carcinogenic substances over a period of decades, and found statistically significant associations between that exposure and several cancers. (Ex. G, Hidajat, et al.).

Dr. Lagana's reliance on Hidajat is unfounded — he simply presumes that nitrosamine exposure through inhalation and ingestion are similarly carcinogenic, without conducting any independent analysis. Hidajat also did not account for significant cofounders in the study population – and in fact, Dr. Lagana admits that the rubber workers who were studied were exposed to other risk factors. (Lagana Dep. at 352:13-19). Dr. Lagana's Report does not consider this.

Dr. Lagana similarly fails to consider other confounders in his own analysis. His Report entirely fails to consider the endogenous formation of NDMA in the human body, yet he agrees it is present. (Lagana Dep. at 224:3-8). He attempts to sidestep the issue by qualifying that he “saw widely varying models as to how much endogenous NDMA is produced” (Lagana Dep. at 226:22-227:9), but ultimately, he simply does not include this important factor in his analysis:

Q: In other words, you do not have an expert opinion on [endogenous NDMA formation]; correct?

A: Just to clarify, the question is, on whether endogenous versus exogenous is more or less dangerous?

Q: Yes.

A: *Well, not to a reasonable degree of scientific certainty.*

(Lagana Dep. at 229:2-12)

“[I]n order to successfully opine on general causation ... any expert must account for the findings reached in the full universe of epidemiological studies.” *In re Zoloft (Sertralinehydrochloride) Prod. Liab. Litig.*, 176 F. Supp. 3d 483, 493 (E.D. Pa. 2016), *aff’d sub nom. In re Zoloft (Sertraline Hydrochloride) Prod. Liab. Litig.*, 858 F.3d 787 (3d Cir. 2017). “While the presence of epidemiology does not necessarily end the inquiry, where epidemiology is available, it cannot be ignored. As the best evidence of general causation, it must be addressed.” *Norris v. Baxter Healthcare Corp.*, 397 F.3d 878, 882 (10th Cir. 2005).

Here, Dr. Lagana has started from a biased premise and then hunted for literature to support it. In order to do so, he necessarily employed an unreliable methodology inconsistent with his own research practices. He employed that methodology in an unreliable way, by failing to appropriately weigh key literature, ignoring studies contrary to his preformed conclusions, and employing studies with inapposite exposures and numerous confounders. For all those reasons, his methodology and opinions are unreliable and his opinions should be excluded.

D. Dr. Lagana Offers Unsubstantiated, *Ipse Dixit* Assertions In Lieu Of Reliable Opinions.

As a final methodological defect, Dr. Lagana’s Report contains a number of assertions that he evidently expects to be accepted on his say-so, with no supporting research, literature, or even so much as a meaningful explanation. These statements

are supported by nothing: no research, no literature, no citation, no reasoned explanation. They exist by virtue of his assertion alone.

Dr. Lagana's insistence that his scientific assertions be adopted at face value without methodological support is directly contrary to well-settled law on expert reliability, which requires a demonstrated association between the data and the expert's opinion. "[N]othing in either *Daubert* or the Federal Rules of Evidence requires a district court to admit opinion evidence that is connected to existing data only by the *ipse dixit* of the expert. A court may conclude that there is simply too great an analytical gap between the data and the opinion proffered." *General Electric Co. v. Joiner*, 522 U.S. 136, 146 (1997); *see also Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 608 (D.N.J. 2002) (same).

One glaring example of Dr. Lagana's unsupported *ipse dixit* is his statement that "it is probable that individuals who are predisposed to cancer for any reason (genetic or environmental) have an even greater likelihood of developing cancer following and in part as a result of ingestion of NDMA or NDEA at the levels established for the contaminated valsartan." (Lagana Rep. at 5). Predisposition to cancer for genetic or environmental reasons is a complex topic in which Dr. Lagana has no apparent qualifications and to which he applied no methodology. Likewise, NDMA and NDEA are not the same, and Dr. Lagana has provided no sound methodological or analytical basis why they should be treated the same. Having

failed to undertake any analysis of predisposition to cancer, and any analysis of the alleged causal connection between NDEA, valsartan, and cancer, Dr. Lagana cannot offer opinions on either subject. *See Wehling v. Sandoz Pharms. Corp.*, 1998 WL 546097, at *5 (4th Cir. Aug. 20, 1998) (“conjecture, hypothesis, subjective belief, or unsupported speculation are impermissible grounds on which to base an expert opinion”).

Even more problematic is Dr. Lagana’s insistence that “to the extent NDMA is discussed herein, the conclusions as to NDMA apply to NDEA as well, unless otherwise indicated.” (*Id.*). He appears to base this on his unsupported belief that NDEA “may be the most potent carcinogen of any known nitrosamine.” (*Id.*). More than a mere drafting shortcut, Dr. Lagana’s attempt to extrapolate the results of studies regarding NDMA and apply them equally to NDEA amounts to sleight of hand. In fact, there is a dearth of evidence in the scientific literature demonstrating a causal link between NDEA and cancer — a general lack of both human and animal studies. Accordingly, Dr. Lagana’s report does not contain any discussion of an association between NDEA and any cancer in humans in the scientific literature. This is important because, contrary to Dr. Lagana’s unfounded assumption, NDMA and NDEA are not the same, and Dr. Lagana has provided no sound methodological or analytical basis why they should be treated the same. Simply put, Dr. Lagana can offer no scientific basis to support his opinion that the trace levels NDEA contained

in affected valsartan can cause cancer in humans. Thus, Dr. Lagana should not be permitted to offer this opinion at trial. *See McMunn v. Babcock & Wilcox Power Generation Grp., Inc.*, 2013 WL 3487560, at *15 (W.D. Pa. July 12, 2013) (stating, “[i]f no association between the exposure and the disease is supported by the scientific literature, there is no basis to find a causal relationship exists and the analysis should end there”); *see also* Motion to Exclude Hecht, at section II(A)(4) (discussing application of the Bradford Hill Criteria for determining causation).

II. DR. LAGANA IS NOT QUALIFIED TO OFFER GENERAL CAUSATION OPINIONS OUTSIDE HIS FIELD OF PATHOLOGY.

Finally, it is not surprising that Dr. Lagana has offered unreliable opinions premised on biased assumptions and flowing from flawed methodology, because he is not qualified to offer them in the first place. His opinions in this case are far afield of his actual expertise as a clinical and anatomical pathologist.

Dr. Lagana’s practice in those fields has not equipped him with the necessary education, training, experience, or specialized knowledge to offer general causation opinions regarding whether NDMA or NDEA cause cancer in humans based on investigation and evaluation of epidemiology literature. Plaintiffs have not called upon Dr. Lagana to diagnose cancer from pathology slides or to research gastrointestinal or liver pathology—the stated areas of his expertise. (Lagana Rep. at 2). Instead, they have assigned him the task of reviewing an unfamiliar body of

epidemiology literature outside his field and to opine on a subject matter he has never previously researched or studied. (*Id.* at 1-2).

To render a qualified opinion that will assist the trier of fact, the proffered expert must “possess specialized expertise” on the subject of his or her testimony. *In re Human Tissue Prods. Liability Litig.*, 582 F. Supp. 2d 644, 655 (D.N.J. 2008) (quoting *Pineda v. Ford Motor Corp.*, 520 F.3d 237, 244 (3d Cir. 2008)). Dr. Lagana has no specialized expertise in epidemiology, yet offers opinions exclusively based on his selective review of epidemiology literature. Compounding his lack of qualifications to offer epidemiological and/or cancer causation opinions, he purports to do so for two substances — NDMA and NDEA — with which he has no prior research experience.

Courts around the country have excluded expert causation opinions under similar circumstances when the expert lacks the necessary specialized expertise to render such an opinion. *See, e.g., Aloe Coal Co. v. Clark Equip. Co.*, 816 F.2d 110, 114 (3d Cir. 1987) (holding district court abused its discretion in allowing witness to testify regarding cause of construction equipment fire where witness lacked expertise in engineering or mechanics, construction machinery design, or determining the cause of equipment fires); *Higgins v. Koch Dev. Corp.*, 794 F.3d 697, 704 (7th Cir. 2015) (treating physician not qualified to testify on causation merely due to her status as a pulmonologist); *In re Viagra Prod. Liab. Litig.*, 658 F.

Supp. 2d 950, 960 (D. Minn. 2009) (“Dr. McGwin is an epidemiologist, not a medical doctor. He is not licensed to diagnose the cause of a patient’s vision loss”). Similarly, Dr. Lagana lacks the necessary specialized expertise to render his opinions and should be excluded.

A. Dr. Lagana’s Clinical And Research Practice Does Not Include Specialized Expertise On Questions Of General Causation.

The opinions Dr. Lagana offers in his Report and testimony are far afield of his qualifications. Dr. Lagana is an anatomic pathologist, with a subspecialty in gastrointestinal and liver pathology. (Lagana Rep. at 2; Lagana Dep. at 60:21-61:1). “Anatomical pathology is the study of tissues to determine the diseases present therein; clinical pathology is the study of disease through laboratory examination[.]” *Campbell v. United States*, 250 F. Supp. 941, 942 (E.D. Pa. 1966). Both fields are distinct from epidemiology, which “studies the incidence, distribution, and etiology of disease in human populations” and “is central to the general causation inquiry[.]” *In re Roundup Prod. Liab. Litig.*, 390 F. Supp. 3d 1102, 1116 (N.D. Cal. 2018) (citations omitted). Epidemiology “is the scientific methodology that allows testing of the hypothesis that Substance A causes Effect B.” *Soldo v. Sandoz Pharms. Corp.*, 244 F. Supp. 2d 434, 533 (W.D. Pa. 2003).

Dr. Lagana likewise admits he lacks expertise in epidemiology, biostatistics, cancer biology, toxicology, hypertension, molecular pathology, oncology, pharmacology, FDA, and regulatory issues. (Lagana Dep. at 64:16-24, 123:15-25,

137:8-10, 157:18-23, 163:15-164:4, 208:18-20, 235:19-236:16). He should be excluded from offering any opinions in these specialized areas of expertise.

Dr. Lagana reviews biopsies and resections removed from patients and provides, analyzing the organs and cells using a microscope and reporting on the histology slides to the patients' care teams, so that they may render the ultimate diagnosis and potentially determine cause. (Lagana Rep. at 2; Lagana Dep. at 79:1-80:2, 60:21-61:1, 61:12-18). The purpose of such review is to make a diagnosis on the tissue, "as to whether something is benign, malignant, inflamed, normal." (*Id.* at 68:3-25). At least 75 percent of Dr. Lagana's time is spent on such review, and only 10 percent of these slides are cancer slides. (Lagana Rep. at 2; Lagana Dep. at 61:12-18, 162:5-19). Dr. Lagana's original research work is likewise confined to the field of pathology, with a focus on gastrointestinal and liver pathology. (Lagana Rep. at 2).

Here, Dr. Lagana reviewed no biopsies or resections, received and examined no slides, studied no tissue specimens, issued no pathology reports, made no determination of whether a sample was benign, malignant, inflamed, or normal, searched, reviewed no pathology literature, and undertook no pathology research. Indeed, the word "pathology" is nowhere to be found in his Report outside of the summary of his qualifications. (*See* Lagana Rep. at 3-33). Nor is any pathology source or journal cited in his references. (*See id.* at 34-37).

Dr. Lagana's experience diagnosing cancer etiology by review of pathology slides in no way qualifies him to opine on whether NDMA or NDEA cause human cancer. Dr. Lagana offers no opinion or testimony that there are any biomarkers in cancer pathology that could ever link NDMA to any cancer cells observed under a microscope. Accordingly, no pathological examination or pathology expertise could be employed to link NDMA or NDEA to cancer generally or to any particular individual's cancer. There are no circumstances where Dr. Lagana's particularized expertise could ever assist the trier of fact to resolve the question of causation based on alleged exposure to NDMA or NDEA in valsartan.

An expert witness is properly excluded "from rendering opinions on subjects outside his field of expertise." *Morse/Diesel, Inc. v. Trinity Industries, Inc.*, 67 F.3d 435, 444 (2d Cir. 1995). Dr. Lagana's analysis falls decisively outside the areas of tissue study and laboratory examination that are within his expertise, and instead consists of his impressions of epidemiological studies he uses to derive opinions on general cancer causation. Citations to epidemiology literature pervade the references in Dr. Lagana's Report. (Lagana Rep. at 34-37). Neither Dr. Lagana's reliance on epidemiology literature purportedly supportive of his conclusions, nor his criticisms of epidemiology literature contradicting his conclusions has any connection to his education, training, experience, or specialized knowledge in the field of pathology.

Dr. Lagana's repeated attempts to pay lip service to the Bradford Hill criteria underscore the problem. (*Id.* at 3, 6, 13, 17, 22, 29, 32, 33). Those criteria comprise a methodology for determining the cause of disease in epidemiology, not pathology. *See In re Roundup*, 390 F. Supp. 3d at 1130 (noting "the Bradford Hill criteria are generally associated with epidemiology"); *In re Breast Implant Litig.*, 11 F. Supp. 2d 1217, 1243 (D. Colo. 1998) ("[T]he accepted method for determining the cause of disease is epidemiology and, if necessary, the Bradford Hill criteria."). Dr. Lagana conceded he incorporated the Bradford Hill criteria into his report, however, in order to avoid "getting into the same argument" as in the *Benicar* litigation— i.e., in order to avoid a challenge to his opinions based on a failure to include the criteria. (*Id.* at 95:14-97:22). That statement is a telling admission of Dr. Lagana's application of a methodology from a separate field and outside his ordinary practice for the sole purpose of securing a perceived advantage in litigation.

Indeed, Dr. Lagana's work and research opining on general causation based solely on literature review is entirely litigation-driven; it is not a subject he encounters in his everyday pathology practice or research. (*See Lagana Dep.* at 118:20-119:5 ("Q: I asked the question, never once in real life, not in litigation have you rendered a causation opinion based purely on articles and not with regard to patients. And you said I have not written a report to that effect; correct? * * * A: Not that I could think of at the moment.")). While he admits the majority of his time is

spent on slide review, he stated at his deposition that he has never looked at any clinical information on valsartan, much less examined a specimen of tissue from a patient in this litigation. (*Id.* at 106:18-24).

Dr. Lagana is simply not qualified to offer the wide-ranging opinions contained in his Report and testimony on general causation with respect to NDMA, NDEA, and certain cancers. The opinions amount to no more than a book report on articles outside his field that he collected and read, with his unqualified take on questions of epidemiology, oncology, biostatistics, toxicology, genetics, and epigenetics—none of which are subjects within his specialized expertise. Critically, *none* of Dr. Lagana’s opinions are based on the principles of pathology, or his clinical practice or research in pathology. Dr. Lagana thus lacks the specialized knowledge to offer the opinions in his Report, and they should be excluded.

B. Dr. Lagana Has Never Studied And Has No Specialized Expertise In NDMA Or NDEA.

Compounding Dr. Lagana’s lack of specialized expertise in the relevant field of study, he also lacks any experience or knowledge with respect to the specific subject matter on which he purports to opine: whether the levels of NDMA and/or NDEA allegedly detected in valsartan can increase an individual’s risk of cancer. Not only has Dr. Lagana stepped outside of his field to opine on that issue, he admits his experience researching cancer causation, NDMA, and/or NDEA is exclusively limited to this litigation. (Lagana Dep. at 164:17-165:5, 260:13-22). In fact, Dr.

Lagana concedes he learned about cancer causation and NDMA or NDEA “largely by doing research for this litigation.” (*Id.* at 53:21-54:9). When questioned on the subject at his deposition, he admitted he has never researched NDMA, NDEA, or valsartan outside this case. (*Id.* at 164:17-165:5).

While a lack of familiarity with a specific chemical compound or other specialized area is not alone grounds to preclude an expert from testifying about it, Dr. Lagana is applying principles, methods, and literature outside his expertise to chemical compounds outside his expertise in order to offer opinions on a subject matter he has never addressed in his professional life. That combination takes him well outside the bounds of any qualified opinion. A proffered witness must have some “specialized knowledge” regarding the areas of his or her testimony in order to qualify as an expert. *In re Human Tissue Prods. Liability Litig.*, 582 F. Supp. 2d at 655; *Higgins v. Koch Dev. Corp.*, 794 F.3d 697, 704 (7th Cir. 2015) (finding treating physician was not qualified to testify as a causation expert merely due to her status as a pulmonologist where she had no training in toxicology or other relevant areas)

Dr. Lagana’s lack of expertise in cancer causation and/or epidemiology, combined with his lack of familiarity with the relevant chemicals in this litigation, falls well short of that standard. More importantly, his lack of qualifications is apparent when viewed in the context of his unreliable methodology and application

of that methodology to unreliable and cherry-picked data. In short, Dr. Lagana's lack of qualifications in this specialized area resulted in his misapplication of basic science and his overlooking important data. His opinions should be excluded.

CONCLUSION

Dr. Lagana is unqualified to provide his purported general causation opinions, and has failed to provide reliable opinions supported by his standard methodology. Instead, he has offered litigation-driven opinions outside his field, applying a methodology outside his standard methods and employed by him exclusively in the context of litigation to arrive at a preconceived result. For all these reasons, Defendants respectfully request that the Court exclude or limit opinions of Dr. Lagana in whole or in part.

Dated: November 1, 2021

Respectfully Submitted:

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CERTIFICATE OF SERVICE

I HEREBY CERTIFY that on November 1, 2021, I electronically filed the foregoing with the Clerk of the Court by using the CM/ECF system which will send a notice of electronic filing to all CM/ECF participants in this matter.

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